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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/814,371	03/22/2001	Graham McCreath	8117-14	4297

23973 7590 06/28/2005

DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE
18TH AND CHERRY STREETS
PHILADELPHIA, PA 19103-6996

EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/814,371	MCCREATH ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,9 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,9 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/15/05 has been entered.

Claims 1, 3, 5, 9 and 12-14 are pending.

Response to Arguments

Applicant's arguments filed 6/15/05 have been considered but are moot in view of new grounds of rejection.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 1, 3, 5, 9 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garner et al. (US 5,639,940) in view of Lord (US 6,037,457), Holm et al. (1985), Jennissen et al. (DE 4240119) and Eigel et al. (Proc. Nat'l Acad. Sci. USA (1979) 76(5): 2244-48).

Garner et al. disclose the transgenic production of fibrinogen from human or non-human sources in the milk of various livestock (column 2, lines 9-15; column 4, lines 15-20 and lines 30-33). The fibrinogen is recovered from the milk using standard practices such as precipitation, filtration and protein chromatography (column 2, line 65, column 9, lines 23-25). Garner et al. state that it is preferred to produce fibrinogen having a ratio of Aα : Bβ : γ expression units having a ratio in the rang or 0.5-1:0.5-1:0.5-1 (col. 7, lines 15-20). In summary, Garner et al. disclose that the recognized practices for recovering

recombinant fibrinogen from milk comprise precipitation and protein chromatography and teach a preferred ratio of the Aα, Bβ and γ chains for optimal activity. This preferred ratio corresponds to the limitation of high Aα-chain integrity recited in instant claim 1 because degradation of the Aα chain leads to an alteration in the preferred chain ratio which represents intact fibrinogen.

Garner et al. lack the claim limitations regarding precipitating fibrinogen from milk in the presence of one or more of lysine, a lysine analog, or ε-aminocaproic acid, the specific HIC chromatography, and the limitation that the recovered fibrinogen has a high Aα-chain integrity.

Lord teaches that recombinantly produced fibrinogen must be collected and then purified. Lord et al. disclose that the collected medium can be purified by "any known method in the art." These methods include precipitation and HIC chromatography(column 6, lines 36-52). Lord et al. also emphasize the need to include protease inhibitors such as epsilon-aminocaproic acid in the concentrating step (precipitation) and/or the purification step. The protease inhibitor prevents degradation of the recombinant product (col. 8, lines 1-33). Therefore, Lord et al. al. reinforce the disclosure by Garner et al. because both emphasize that recombinant fibrinogen can be purified by well-known techniques in the art, including precipitation and chromatography such as HIC.

Jennissen et al. disclose the purification of human fibrinogen by applying plasma to a hydrophobic interaction column comprising pentyl-Sepharose. The yield of the purification was 25-60%. The purified fibrinogen was molecularly uniform and fully active. The purified human fibrinogen was subjected to SDS gel electrophoresis to characterize the individual chains of the purified fibrinogen. The molecular weight of the human Aα-chain was 72 kDa (col. 5, lines 20-55). Thus, Jennissen et al. demonstrate that HIC chromatography for the purification of fibrinogen is one of the many known purification methods for fibrinogen.

Holm et al. disclose the purification and characterization from human plasma wherein fresh human blood was combined with citrate and precipitated with β-alanine. The precipitate was solubilized and then fractionated step-wise with ammonium sulfate to give three fractions, the high molecular

weight (F1), low molecular weight fraction (F2 and F3, see page 166, first paragraph, for fibrinogen designations). Holm et al. compare the three fractions on SDS-gel electrophoresis and HPLC and note the migratory characteristics of each fraction in the SDS and HPLC methods (p. 169). The subunit chain patterns of the fractions demonstrate that the high molecular weight fibrinogen contained intact Aα-chains and no observable chain remnants compared to the low molecular weight fractions where the degradation of the Aα-chain chain is clearly evident (p. 170, lines 5-7). Therefore, Holm et al. teach that precipitation is a well known technique to purify fibrinogen. Furthermore, Holm et al. demonstrate that it is also well known to employ HPLC to evaluate the relationship between the degradation of the Aα-chain and each of the fibrinogen fractions, wherein the F1 fraction has an intact Aα-chain.

Thus, the combined disclosures by Garner et al., Lord, Jennisson et al. and Holm et al. demonstrate that the application of the known purification methods of precipitation and HIC chromatography were conventional for purifying recombinant and nonrecombinant fibrinogen. Holm et al. also teaches the importance of evaluating the purified fibrinogen for F1 fractions for high Aα-chain compared to the F2 and F3 fractions.

Eigel et al. disclose that plasminogen was found in bovine milk and found to be identical to fibrinogen obtained from plasma. Eigel et al. teach that proteases such as plasmin are naturally occurring in mammalian milk. The discovered that autoproteolysis of the fibrinogen occurred during the purification from milk. The addition of a protease inhibitor, epsilon-aminocaproic acid, inhibited the lysis (abstract and left column of p. 2244).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to purify fibrinogen from a transgenic animal milk source by employing precipitation and/or HIC chromatography along with a protease inhibitor to obtain a fibrinogen fraction having high Aα chain integrity. The ordinary artisan would have been motivated to do so because the combined disclosures by Garner et al., Lord, Jennisson et al. and Holm et al. demonstrate that the application of the known purification methods of precipitation and HIC chromatography were conventional in the art for purifying

recombinant and nonrecombinant fibrinogen. The combined references make it clear that the ordinary artisan would have known that precipitation, separation, and HIC are all suitable methods of purifying fibrinogen and that said methods can be done singly or can be combined to achieve the desired level of purification. The ordinary artisan would have been motivated to specifically apply the claimed step to the purification of plasminogen from milk because proteases are endogenous to milk and are known to degrade fibrinogen in a milk milieu, thereby decreasing the product yield. The ordinary artisan would have had a reasonable expectation of success that fibrinogen could be purified from milk using the conventional steps of precipitation and/or HIC chromatography in the presence of a protease inhibitor because the combined disclosures showed that these methods were successful for purifying fibrinogen from various sources, including milk.

The ordinary artisan would have reasonably expected to obtain fibrinogen having high Aα-chain integrity when purifying fibrinogen by a combination of precipitation with ε -aminocaproic acid and HIC chromatography. Both Holm et al. and Jennissen et al. established that fibrinogen having high Aα-chain integrity can be obtained by employing precipitation or HIC chromatography *independently of one another.* Using only a precipitation step, Holm obtained fibrinogen with an intact Aα-chain integrity. Using only HIC chromatography, Jennissen et al. isolated fibrinogen having an Aα-chain with a molecular weight of 72 kDa. Based on the molecular weight taught by Holm et al., this value is within experimental error and the chain is intact. However, one of ordinary skill in the art would judge an intact chain to have high integrity. Given that both methods independently yield fibrinogens with intact Aα-chains, the ordinary artisan would have reasonably foreseen that the combination of the methods to yield fibrinogen having high Aα-chain integrity.

In conclusion, it would have been obvious to the ordinary artisan to combine well known purification methods to purify fibrinogen to obtain a fraction with high Aα-chain integrity. Further, it would not have been surprising to the ordinary artisan to obtain fibrinogen having high Aα-chain

integrity based on a conventional methods. Therefore, the claims are prima facie obvious over the cited prior art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Susan Hanley
Patent Examiner
AU 1651

JEAN C. WITZ
PRIMARY EXAMINER